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Case Title

Using the Medical Research Council framework for developing and evaluating complex interventions – Mindfulness-based interventions for people with multiple sclerosis

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Physical Medicine and Rehabilitation [SD-MD-23]

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Advanced Undergraduate

Contributor Biographies

Robert Simpson is a Clinical Assistant Professor in Physical Medicine and Rehabilitation at the University of Toronto, Canada. Robert's clinical background and qualifications include completion of vocational training in General Practice and Rehabilitation Medicine, with fellowship training in Integrative Medicine. Robert's research focus is developing and evaluating complex interventions for people with multimorbidity and complex disabilities. His PhD thesis focused on the development and evaluation of mindfulness-based interventions for people with multiple sclerosis.

Stewart Mercer is a Clinical Professor in Primary Care and Multimorbidity in the Usher Institute at the University of Edinburgh, Scotland, and the Director of the Scottish School of Primary Care (www.sspc.ac.uk). He is recognized as an international leader in research on multimorbidity, and regularly publishes in high impact journals including the Lancet and the BMJ. He has published over 250 research papers, numerous book chapters and reports, and two books.

Published Articles

Simpson, R. J., McLean, G., Guthrie, B., Mair, F., & Mercer, S. W. (2014). Physical and mental health comorbidity is common in people with multiple sclerosis: nationally representative cross-sectional population database analysis. *BMC neurology*, 14(1), 128.

Simpson, R., Booth, J., Lawrence, M., Byrne, S., Mair, F., & Mercer, S. (2014). Mindfulness based interventions in multiple sclerosis-a systematic review. *BMC neurology*, *14*(1), 15.

Simpson, R., Mair, F. S., & Mercer, S. W. (2017). Mindfulness-based stress reduction for people with multiple sclerosis—a feasibility randomised controlled trial. *BMC neurology*, *17*(1), 94.

Simpson, R., Byrne, S., Wood, K, Mair, F.S., & Mercer, S. W. (2018). Optimising mindfulness-based stress reduction for people with multiple sclerosis. *Chronic illness*, *14*(2), 154-166

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Simpson, R., Simpson, S., Ramparsad, N., Lawrence, M., Booth, J., & Mercer, S. W. (2019). Mindfulness-based interventions for mental well-being among people with multiple sclerosis: a systematic review and meta-analysis of randomised controlled trials. *Journal of Neurology, Neurosurgery & Psychiatry*, *90*(9), 1051-1058.

Simpson, R., Simpson, S., Ramparsad, N., Lawrence, M., Booth, J., & Mercer, S. (2019). Effects of Mindfulness-based interventions on physical symptoms in people with multiple sclerosis—a systematic review and meta-analysis. *Multiple Sclerosis and Related Disorders*, 101493.

Abstract

People with disabling long term conditions often require rehabilitation to help them function optimally in society. Rehabilitation is by definition a complex intervention, meaning multiple factors can influence the outcomes we see following treatment. With multiple factors at play, trying to understand the effects rehabilitation treatments have on people is challenging. This matters clinically, when considering the effectiveness of existing treatments, but also academically, when designing new interventions. The UK Medical Research Council has a framework to help guide researchers through the process of designing and evaluating complex interventions. We used this to evaluate the potential use of a mindfulness-based intervention for people with multiple sclerosis. This paper describes that process, our experiences and findings. We used a mixed-methods approach, including quantitative epidemiological work, a systematic review and meta-analysis, and a feasibility randomized controlled trial (RCT), complemented by qualitative interview data from study participants to help us better understand why we were seeing what we were, and help us improve the mindfulness intervention, making it more relevant and accessible to those taking part. We found a clear need for novel and effective psychosocial interventions to help people with multiple sclerosis deal with stress and disability. We also identified that no clear optimal mindfulness-based intervention approach exists in this context. We thus tested a standard mindfulness-based intervention in a group of people with multiple sclerosis and used their feedback to improve the course. The next stage for this work would be to test the optimized intervention in a full-scale RCT.

Learning Outcomes

By the end of this case, students should be able to:

- 1) Define what is meant by a ‘complex intervention’
 - 2) Describe the five steps recommended by the MRC when developing and evaluating complex interventions
 - 3) Describe at least one clear advantage of using a mixed methods approach to research in this area
 - 4) Describe one method for assessing ‘quality’ in randomized controlled trials
 - 5) Understand the concept and application of researcher ‘reflexivity’ to minimize bias in qualitative research
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Case Study

As clinicians, most of the treatments we use are by definition ‘complex interventions’ (Craig, 2008). The UK Medical Research Council (MRC) defines complex interventions as having ‘*several interacting components*’, where multiple factors may be leading to the effects we see following treatment (Craig, 2008; MRC, 2008). An oft quoted example is rehabilitation following stroke. Good quality evidence supports multidisciplinary rehabilitation following a stroke as effective; we may recommend it for our patients. But, if asked how or why and for whom does it work, many of us may struggle to give a clear response. We might say ‘*Well, physiotherapy helps people recover their limb function and mobility*’, or ‘*Occupational therapy helps people with a hemiplegia learn to care for themselves*’, or ‘*Some antidepressant drugs improve patient outcomes*’, but the reality is that rehabilitation is an umbrella term for a process, not an event, whereby concerted efforts are made by care providers to minimize disability and optimize function (santé & Organization, 2001). It is

highly probable that no one factor makes rehabilitation successful, or not (Langhorne, Bernhardt, & Kwakkel, 2011). The same applies even in the case of drug treatments (Kaptchuk & Miller, 2015). Contextual factors such as individual patient and prescriber variability impact on observed effects. Considering this, it makes sense to think about these factors when we treat patients, but also when we develop new treatments.

In 2012, I enrolled in a PhD programme as part of an intercalated clinical-academic training programme in Rehabilitation Medicine in the United Kingdom. I was interested in how people cope with long term and disabling conditions. My career interests and trajectory were heavily influenced by the work of Professor V.S. Ramachandran in California (Ramachandran, Blakeslee, & Shah, 1998) and I wanted to develop my skills as an investigator, to complement my clinical learning as a specialty trainee. Much of my first year of specialty training was spent working with people with multiple sclerosis. I was aware through my clinical work that stress, anxiety and depression were important factors in my patients' lives, and from various Cochrane reviews that effective treatments were limited, mainly comprising cognitive behavioural therapy and antidepressants, the latter's use frequently limited by troublesome side effects (Koch, Glazenborg, Uyttenboogaart, Mostert, & De Keyser, 2011; Thomas, Thomas, Hillier, Galvin, & Baker, 2006). I had heard of a treatment called 'Mindfulness' for treating stress, but knew nothing practically of its use, let alone what role it might have in helping people with multiple sclerosis. After reading up on mindfulness, I learned that a Professor at Glasgow University, Stewart Mercer (co-author), was already researching mindfulness in other patient populations. Professor Mercer agreed to meet, and it quickly became clear that we had similar interests. He agreed to take me on as a PhD student and suggested I start out by reading the MRC framework for developing and evaluating complex interventions (MRC, 2008). He also requested I produce a Gantt chart –

in brief, a chart outlining anticipated windows of time for project completion, where there are multiple research strands running simultaneously. It is harder to do than it sounds, and it is not set in stone.

The MRC guidance on complex interventions describes an iterative, multi-faceted approach to developing and evaluating new treatments in healthcare (MRC, 2008); due to be updated in 2019. The 2008 framework acknowledges complexity as the norm in healthcare and proposes that in order to address complex research questions, a mixed-methods approach is advisable. For example, if we were to go straight to testing the effectiveness of a mindfulness-based intervention among people with multiple sclerosis for improving stress, anxiety and depression, were we to find that it wasn't effective we would have no real way of knowing why. In this case, it would be short sighted to discard the intervention at this point, particularly if we already knew it was effective in other conditions (it is!). Instead, the MRC framework suggests working towards a definitive test of effectiveness, through detailed and iterative preparatory feasibility work, before proceeding to a full-scale randomized controlled trial (RCT).

MRC Step 1 – Defining your study population

The MRC framework suggests that researchers should set out to define the population of interest as a first step in feasibility research. Doing so has various advantages and helped us shore up our research ideas. For example, before rushing in to see whether mindfulness-based interventions were effective in helping people with multiple sclerosis manage stress, anxiety and depression we wanted to be sure that these factors were indeed a problem in the MS population, rather than proceed on a purely anecdotal basis; there is clearly no sense in developing an intervention for a population where there is no need.

Epidemiology can be defined as the study of how often diseases occur in a specified population and why (Coggon, Barker, & Rose, 2009). In order to determine whether stress, anxiety and depression were indeed common in people with multiple sclerosis we had to consider incidence and prevalence. In this context, incidence refers to the rate a condition occurs in a given population over a specified period of time (often number of cases/year), whereas prevalence refers to the proportion of a population affected by a condition at a given point in time (Coggon et al., 2009). Measuring incidence requires a longitudinal approach, whereas prevalence can be cross-sectional; a ‘snapshot’ overview at a single point in time. As we were not seeking to identify the rate of occurrence of stress, anxiety and depression in people with multiple sclerosis, but rather how many were affected by these conditions at a given time, measuring prevalence made sense for our study.

For complex reasons, Scotland has among the highest incidence and prevalence rates for multiple sclerosis worldwide (Koutsouraki, Costa, & Baloyannis, 2010). Multiple sclerosis is an expensive condition to manage (Naci, Fleurence, Birt, & Duhig, 2010) and is one of a number of long-term conditions prioritised by NHS Scotland. Through Professor Mercer’s research on multimorbidity (the occurrence of more than one long term condition in an individual, without any condition ordered as more or less important), we had access to a primary care database, which was nationally representative, meaning that although not everyone in Scotland was included, there were enough (~1.8 million) to extrapolate findings as indicative of likely true population level findings. Multiple sclerosis was one of 40 long term conditions included in the database, as were anxiety and depression. We were thus able to use multiple sclerosis as an ‘index’ condition and compare the prevalence of ‘comorbid’ anxiety and depression in this population (~4,000 subjects with multiple sclerosis) versus

controls (~1,200,000). We used logistic regression to do this, a statistical technique that accounts for multiple variables when comparing two groups and generates odds ratios that indicate the likelihood of having a condition versus not, depending on whether a subject has, for example, multiple sclerosis, or not (Harris & Taylor, 2014).

Besides having to learn about the statistical method, which was new to me, this undertaking was not as straightforward as it might sound. The database was not designed for our study and the data first required ‘cleaning’. For example, there was a group of patients that had to be found and excluded as they were duplicates and, as mentioned, we decided to exclude those aged under 25. We used a data management programme called Statistical Package for the Social Sciences; again, new to me, which required training to use that was, let’s say, ‘ad hoc’. Learning how to organise the data in such a way that I could generate the results we required wasn’t easy and I had several on the spot tutorials from other researchers around the department, all of whom had their own stories of how they learned to use the programme. Each researcher suggested a different textbook. There were Glasgow University sponsored practical tutorials in using the programme, which were not helpful, aimed at a far more basic level of programming and research design, with class tutors unable to give advice on specific projects. In the end we recruited an experienced quantitative researcher to check the statistics I was generating, which was time consuming, but worth it as I was able to spot mistakes when pointed out by a more experienced researcher, and ultimately, we were keen to publish.

Our analysis, which was the first of its kind from Scotland, showed that multiple sclerosis patients residing in Scotland were three times more likely to be affected by comorbid anxiety and depression than those without and were twice as likely to have other physical comorbidities. Further, as the number of additional physical conditions (physical

‘comorbidities’) besides multiple sclerosis rose, so did the prevalence of mental health impairment (mental ‘comorbidity’; mainly anxiety and depression). This fitted with contemporary research in comorbidity more generally, a literature which also describes being comorbid as stressful (Fortin et al., 2006). The value of our findings was that they confirmed that, at a population level, there was a high prevalence of anxiety and depression in people with multiple sclerosis in Scotland – so, not just an anecdotal finding from clinic (R. J. Simpson, McLean, Guthrie, Mair, & Mercer, 2014).

Section summary

When researching complex interventions, it is important to start by clearly defining your study population, as:

- This provides a clear focus for subsequent research questions
- Can help clarify areas of unmet need within a population

MRC Step 2 – Defining your intervention

In part, mindfulness-based interventions derive from ancient Buddhist and Yogic meditation techniques, designed to transcend limited views of the self and associated suffering. In the late 1970’s in North America, John Kabat-Zinn collated methods from these ancient meditation techniques with contemporary psycho-education materials to create Mindfulness-based stress reduction (MBSR) (Kabat-Zinn, 1982), a group programme designed to mitigate pain and stress in those with long term conditions. MBSR (and a derivative, Mindfulness-based cognitive therapy (Segal, Williams, & Teasdale, 2002)) has since been applied widely in various health populations, with good quality evidence for treating people with stress, anxiety, and depression (Fjorback, Arendt, Ørnbøl, Fink, & Walach, 2011). What wasn’t

known was whether MBSR or its derivatives were effective in treating stress, anxiety and depression in people with multiple sclerosis.

The MRC framework recommends that when seeking to define what is known about the effectiveness of a given healthcare intervention in a population of interest, researchers should seek out a systematic review, if available. A systematic review of RCTs is widely regarded as the highest form of evidence (Harrison, Kulkarni, Baguneid, & Prendergast, 2009). We thus performed a strategic scoping search of the literature using simple keywords like ‘multiple sclerosis’ and ‘mindfulness’ to see if such a review already existed. We couldn’t find one and our preliminary search did not reveal much in terms of RCT evidence either. We wanted to be sure and thus set out to develop a plan to carry out a systematic review, a more rigorous assessment of the literature. We had to think carefully what our limits would be, as we were working around the set timescale of a full time UK-based PhD, meaning three full years to collect new data, and a year in ‘thesis pending’ for write up. Professor Mercer had recently contributed to a systematic review on the effectiveness of mindfulness-based interventions for people who had suffered from a Stroke and we made contact with that study’s lead/co-authors’ and suggested to work together on our proposed systematic review looking at mindfulness-based interventions for people with multiple sclerosis; thankfully, they agreed. This time I would take the lead role, supported by the team members as necessary. I had to draw up a protocol for a systematic review registry; not essential, but widely and increasingly seen as good practice for any new systematic review. In the UK, this meant the Centre for Reviews and Dissemination, University of York. Arguably, doing this helps researchers (especially novice) to meet basic review requirements and other quality markers, demonstrating awareness of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidance, setting a clear research question, developing a pre-defined search

strategy, inclusion-exclusion criteria, data extraction technique and materials, quality appraisal technique(s), and plan for data syntheses, depending on what is available (i.e. a narrative format versus meta-analysis). It also helps prevent unnecessary duplication if a review already exists or is underway. Our systematic review protocol can be found here: <https://www.crd.york.ac.uk/prospero/>

We anticipated it would take three months to complete the literature search, data extraction and preliminary write up of the manuscript for the systematic review – we wanted to publish, and thought it likely, as there were no previous reviews in this area. However, a lot depended on the size of the literature. From our scope of the literature we thought it would be small, but if there turned out to be very many studies, the review process might take longer. In the event, there were only three papers; two RCTs and a controlled trial. This meant data extraction and synthesis was relatively straightforward, bearing in mind that much of this is pre-specified in the protocol. There wasn't enough data to produce a meta-analysis, so the review format was narrative.

Our narrative systematic review found that each study used a different mindfulness-based intervention, complicating interpretation of results. None evaluated the impact of a mindfulness-based intervention on stress, but all reported on effects on anxiety and depression. They also reported on fatigue, pain and dynamic balance, outcomes we had not anticipated. Our synthesis suggested a beneficial effect on all of these outcomes. However, study quality is an important consideration in research such as this; if we see impressive effects on outcome measures it is important to step back and ask how reliable the findings are, especially if we are to make any recommendations to clinical colleagues or to our patients. There are various methods for assessing quality in clinical trials, depending on study

design i.e. RCT vs observational pre-post (see www.equator-network.org). We used the Cochrane Collaboration tool for RCTs (Higgins et al., 2011; Sterne et al., 2019) (updated recently (Sterne et al., 2019)), which assesses measures taken in trial conduct to minimize bias (Table 1). In short, the less potential for bias, the higher the quality. In some ways it is an easy tool to use, but it depends on understanding certain terms relating to trial conduct, such as sequence generation, allocation concealment, blinding, completeness of outcome data and selective outcome reporting. From my experience during the PhD and since then, I have found that there is particular scope for misinterpretation of the Cochrane criteria when it comes to what is meant by ‘incomplete outcome reporting’ and ‘selective reporting’. One way to protect against misinterpretation of terms is to have multiple reviewers assess bias and compare/discuss discrepancies. In the event, we didn’t need to do this, but looking back, I’m not sure I fully understood those terms then; I’m still learning more about them even now.

Table 1 – Cochrane Collaboration tool for assessing risk of bias in RCTs (Reproduced with permission from: (Higgins et al., 2011))

Bias domain	Source of bias	Support for judgment	Review authors' judgment (assess as low, unclear or high risk of bias)
Selection bias	Random sequence generation	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups	Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence
	Allocation concealment	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen before or during enrolment	Selection bias (biased allocation to interventions) due to inadequate concealment of allocations before assignment
Performance bias	Blinding of participants and personnel*	Describe all measures used, if any, to blind trial participants and researchers from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective	Performance bias due to knowledge of the allocated interventions by participants and personnel during the study
Detection bias	Blinding of outcome assessment*	Describe all measures used, if any, to blind outcome assessment from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective	Detection bias due to knowledge of the allocated interventions by outcome assessment
Attrition bias	Incomplete outcome data*	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomised participants), reasons for attrition or exclusions where reported, and any reinclusions in analyses for the review	Attrition bias due to amount, nature, or handling of incomplete outcome data
Reporting bias	Selective reporting	State how selective outcome reporting was examined and what was found	Reporting bias due to selective outcome reporting
Other bias	Anything else, ideally prespecified	State any important concerns about bias not covered in the other domains in the tool	Bias due to problems not covered elsewhere

*Assessments should be made for each main outcome or class of outcomes.

A key finding from our systematic review was that, although likely beneficial, no clear optimal mindfulness-based intervention existed for people with multiple sclerosis. It also wasn't clear what role multimorbidity and/or disability might play in participation i.e. most studies did not explicitly consider comorbidity and were only including those with fairly low levels of impairment (R. Simpson et al., 2014).

Section summary

When researching complex interventions, it is important to be clear about what is/is not known about the intervention in the population of interest. One method of doing this is to conduct a systematic review, which has the following advantages

- Offers a structured, auditable process for identifying relevant literature, analysing findings, assessing quality of evidence and reporting results
- Offers flexibility with regards to presentation style; a narrative review or meta-analysis, depending on data generated

MRC Step 3 - Testing your intervention

The MRC framework recommends testing a new intervention for 'feasibility' in a given population before moving to a full-scale study. Practically, this means identifying what you think the intervention should comprise and then testing it in a smaller scale study to see how people experience it and what effects it has. The MRC framework allows for a flexible and iterative approach when it comes to designing/deciding upon intervention format, components, and outcome measurement. It is important to get these things right before moving on to a full-scale (and likely expensive) RCT and research funding bodies like the National Institute for Health Research will look to see that this has been done before approving funding: <https://www.nihr.ac.uk/>.

In our case, we wanted to know how feasible it would be to deliver a mindfulness-based intervention to people with multiple sclerosis with a wider range of impairments and disability than had been previously reported. Inherent in this, we wanted to find out how acceptable and accessible people with multiple sclerosis found the intervention, whether they'd be willing to take part in a RCT, whether they'd adhere to the recommended 'dose' and how likely effective the intervention was at improving outcomes of interest (stress, anxiety and depression). To do all of this, we knew we would have to use a mixed methods approach; quantitative, testing the likely effectiveness of a mindfulness-based intervention, qualitative, with participant interviews to better understand why we were seeing the level of participation, adherence and effects associated with the intervention. As our systematic review had not identified an optimal mindfulness-based intervention in this context, we opted for MBSR, a standardised approach (we chose this over mindfulness-based cognitive therapy as the latter was designed specifically to offset recurrent depression and we were interested in effects on stress, anxiety and depression; MBSR had supportive evidence for effectiveness in all three in non-MS populations).

The MRC framework is not proscriptive at this stage but allows researchers' multiple potential options. For example, we could have simply tested MBSR in a pre-post- study, still being able to collect the majority of the data we needed to work-up to a full-scale trial. However, we felt it was also important to test trial procedures at this stage, i.e. could we recruit, randomise, retain and follow up? (i.e., Would people be willing to wait a number of months to receive MBSR?). Through discussion, we had decided it was unethical to offer only the chance of receiving MBSR, and thus that everyone taking part in the study would eventually receive the intervention. This seemed optimal, but generated additional cost for a

second MBSR group, no small undertaking as the course comprises eight weekly sessions, requires a suitable location for a group of participants, materials and instructors for that duration. However, we also knew this approach would bring an additional advantage in that it would allow us to test any changes we made to MBSR following feedback from the group randomized to receive it in the RCT.

Next, we had to decide on the sample size for the RCT. Sample size refers to how many people take part in a study, and in full scale RCTs is determined by statistical ‘power’ tests that take into consideration things like how many participants are likely to complete outcome measures by the end of the trial, what sort of effect sizes are anticipated, and how meaningful are these clinically. We didn’t have that data at this stage. There isn’t any definite guidance in the literature on what constitutes optimal group size for a mindfulness-based intervention. From discussion with the local NHS instructors, who we hoped would deliver the course, we knew that most of their groups had around 15 participants, up to a maximum of 20. We discussed whether 30 people would be enough, or whether we’d need to run more than one MBSR course for the RCT. We didn’t have funding to do this on top of the additional course we had planned for our controls at study completion. We sought the advice of a statistician, who advised that 20 per group would be good, but 25 would be better. We had to check with the instructors if they would be willing to work with a larger group. They were but expressed concern that space might be tight. We decided to go with 25 per group (50 people in total). This was to come back to haunt us later.

We were planning to test MBSR against care as usual. The MRC framework suggests this is the optimal approach at this stage. We were not looking to compare against any other treatment (despite the evidence for cognitive behavioural therapy, there is no current ‘gold

standard' in this context). The MRC suggests that while still developing an intervention, testing against an active comparator can complicate interpretation of findings.

Our next step was to produce a written protocol. This would put our 'mark down in the sand', so to speak, as it would be published online via a clinical trials registry (a prerequisite), and as we were planning to recruit from NHS sites and carry out the research on NHS premises, would go before an NHS ethical review board for approval. The protocol is a hefty piece of work, but it prepares you well for the even heftier NHS ethics application:

<https://www.myresearchproject.org.uk/>. The protocol has to make it plain and clear, as regards what you plan to do, why, how, where, and with whom. The ethical review board is there to protect patients, especially important when considering new interventions. Going before the ethical review board was initially a daunting experience, a room filled with about 30 people, lay and professional, asking questions about our study from a variety of perspectives. However, it quickly became clear that what the Board was seeking to establish was that we were clear and realistic about what we planned to do, that it was safe, and that we understood our responsibilities towards participants'. In this sense, it was a positive learning experience and served to shore up ideas.

With ethical approval granted, we were free to start recruiting, something we had allotted (optimistically) three months for on the Gantt chart; for complex reasons, most complex interventions fail to recruit to target (Craig, 2008). In our case, the first fortnight was true to form. I had naively anticipated clinical colleagues in rehabilitation, neurology and general practice would freely refer patients, but in the event very few were forthcoming (something we would explore later in qualitative interviews). We had to meet quickly as a research team and decide how to address the shortfall. We agreed I would approach the multiple sclerosis

Specialist Nurses at the local tertiary care centre and ask for their help. The Specialist Nurses could not have been more helpful, immediately seeing the value in finding additional stress management resources for their patients. Within a further two months we were fully recruited, oversubscribed even. The trial could go ahead as planned and the first MBSR group took place shortly thereafter. From a personal perspective, this also meant my PhD thesis remained on track.

We were assessing a suite of outcome measures for the trial, including stress, anxiety, depression, cognitive function, fatigue, pain, mindfulness process markers, and emotional lability. This was because, following the systematic review and related literature, we had several ideas about where a mindfulness-based intervention might help and how it might work. Through trial and error, we found that it took some participants over an hour to complete the forms. This was in itself an important finding, when considering whether trial procedures are feasible i.e. are people able/willing to fill out a battery of measures? Despite this we had a good rate of return (>80%), throughout the trial, and this data subsequently allowed us to determine likely effectiveness. We found significant improvements in stress, anxiety, depression and certain aspects of cognition, although the beneficial effects on stress and depression were short lived (evident post-MBSR, but less so at three months follow up), raising important questions about treatment stability/sustainability, not answerable through simple quantitative observations. We also observed that although most people continued to fill out measures through the study, adherence to prescribed MBSR treatments or ‘dosing’ was sub-optimal (Robert Simpson, Mair, & Mercer, 2017). As ‘dose’ is known to mediate beneficial effects for mindfulness-based interventions (Parsons, Crane, Parsons, Fjorback, & Kuyken, 2017), we knew that exploring this via our qualitative interviews could potentially throw light on the reasons why.

We carried out participant and instructor interviews following the first iteration of MBSR and then again, with another group of participants, instructors and clinicians' routinely working in the multiple sclerosis field, following the second iteration of MBSR (i.e. after the RCT was completed). We had preconceived hypotheses about how people with multiple sclerosis might experience MBSR, expecting that multimorbidity and/or disability might limit participation, but we also wanted to explore participant experience in its own right. Thus, we had to use a qualitative research method that was flexible enough to cover such a wide remit, practical, in that we were not seeking to develop a new theory but instead organise and describe what we were seeing, and general enough, so that it could be used in subsequent, secondary analysis looking at barriers and facilitators to implementation (as recommended by the MRC framework).

We chose to use the Framework Approach to Thematic Analysis (Ritchie & Spencer, 2002). The advantages of this were it being relatively user friendly for the novice researcher (not requiring a particular 'stance' on epistemology), structured, in that it helped with organisation of data (from a total of 47 interviews), and was already widely used and accepted as a valid method in healthcare research (Smith & Firth, 2011). As this was a PhD study, funding was limited, and this meant that I carried out the majority of interviews myself, then analysed the data together with Professor Mercer and my second supervisor, Professor Frances Mair. The obvious downside to this is the potential introduction of researcher bias and I had to learn to respond 'reflexively' when interviewing and when interpreting the data (Mays & Pope, 2000). As a physician, I had pre-existing ideas and likely unconscious bias towards what participants might say. I had to actively work to stop myself from doing this, reminding

myself repeatedly of my potential for preconceived values and ideas influencing my questioning and judgement; but, in all likelihood, bias probably crept through despite this.

Our analysis of the interview data generated four main overarching themes, namely what it was like for people with multiple sclerosis to come together as a group for MBSR, what it was like to practise the meditation techniques, what were the perceived effects, and how could the course be improved. We used the findings to optimize the second MBSR course, after the trial was completed, and then interviewed participants from the second course to assess the impact of these changes. We then used all of our thematic analysis data to assess implementability of MBSR for people with multiple sclerosis. Thus, as the study progressed, we moved from an 'inductive' to a 'deductive' approach, whereby as our knowledge grew, we were able to hone our approach to answer more specific questions.

I really enjoyed the qualitative part of the research project, as I liked listening to participants talk about their experiences, which challenged my assumptions (bias), and what they said spread light on some of the unanswered questions from the trial. For example, people spoke about why they had come on the course, what sustained their involvement or led to their dropping out (a group of 25 people was too many for some!), and how participants used the MBSR techniques in their day to day lives (many spoke about how it improved their relationship with themselves and with others'). Participant feedback also identified a need to avoid mindfulness jargon and that the application of a standardised course in this context had clear limitations (R. Simpson, Byrne, Wood, Mair, & Mercer, 2018).

Section summary

When developing and evaluating complex interventions it is important to test feasibility before proceeding to a full-scale trial. Aspects of feasibility testing include both quantitative and qualitative components, such as:

- Trial procedures, such as recruitment, randomization, retention and follow-up (quantitative)
- Level of treatment adherence observed (quantitative)
- Likely effectiveness (quantitative)
- Acceptability and accessibility to participants (qualitative)
- Need for intervention and/or outcome tailoring and optimization (qualitative)

MRC step 4 – Implementation

The MRC framework suggests assessing barriers and facilitators to implementation, from an early stage. This is so as to prevent changes being made at a late stage in the research process, when funding is committed, or further downstream when an intervention has been adopted into widespread clinical practice. We used Normalization Process Theory to assess implementability (May, 2006). Normalization Process Theory was one of a range of options suggested by the MRC, but as Professor Mair was expert in its use, using it was an easy decision to make. I was worried though, as the submission deadline for my PhD thesis was rapidly approaching. I didn't think I'd manage another qualitative analysis (my Gantt chart was running out of space!), but it turned out that as this was a secondary analysis (using data we had already generated and analyzed), it was a simple case of categorizing data under pre-defined Normalization Process Theory criteria. It was at this point that the extra qualitative data, from the MBSR instructors and multiple sclerosis clinicians became especially relevant, as Normalization Process Theory is designed to help ascertain how complex interventions become embedded in routine clinical care. It was apparent that most of the clinicians, whilst

supportive of the concept, had a limited knowledge of mindfulness-based interventions. It was also clear that extra work would be required to gain support for its use in existing treatment pathways, and that whilst clinicians would support treatments that their patients reported benefiting from, having a robust evidence base also mattered a lot to them (R. Simpson, Simpson, Wood, Mercer, & Mair, 2018).

Section summary

When researching complex interventions, it is important to consider implementation from an early stage. Practically, this can mean:

- Exploring potential barriers and facilitators to eventual implementation through specific questioning during qualitative interviews with key stakeholders (for example, participants, clinicians, and those delivering the intervention)
- Using a validated implementation tool to assess implementability via a secondary analysis of study data corpus (quantitative and qualitative)

Stage 5 – Reporting

The fifth stage in the MRC framework process is reporting of findings. Practically, this meant doing several things, to include publication in the academic literature, presenting at conferences, and feeding back to study participants. For me personally, it also meant a looming PhD viva.

It is important to point out that this is not in fact, however, the final stage of the MRC process. The process is ongoing and iterative. For example, we've since updated our systematic review, this time being able to perform a meta-analysis ((Robert Simpson et al., 2019; R. Simpson et al., 2019)). The MRC framework is designed to help researchers

produce the necessary findings that lay the groundwork for a full-scale trial, or not if it becomes clear that proceeding is likely to be unsuccessful. Our findings of likely effectiveness were encouraging, as was the majority of participant feedback. Our feasibility data had also generated the information we needed to estimate likely attrition and required sample size.

We reported the findings from this body of work in a series of publications. This process opened up the work to rigorous academic peer review, serving to hone thinking further, and shape future research ideas and planning. As things stand, we are now in a very strong position to proceed to a funding application for a full-scale RCT, likely testing our optimized MBSR course against a matched cognitive behavioural therapy intervention, and against usual care, the latter so that we can also assess likely health economic benefits. Watch this space!

Section summary

Reporting is an important part of developing and evaluating complex interventions, whereby:

- Findings are opened up to external scrutiny and valuable peer review
- Findings can be used to justify proceeding to a full-scale trial, or not
- Findings can demonstrate to funding bodies that applicants are capable of seeing through to completion the complex processes of running a clinical trial

Conclusion

We used the MRC framework for developing and evaluating complex interventions in healthcare to assess the utility of mindfulness-based interventions for people with multiple sclerosis. Following this framework, we began with epidemiological work, moved on to a

systematic review, and then a feasibility RCT with a parallel qualitative process evaluation. All this took the best part of three years, ultimately forming the basis of a PhD thesis. It involved a multidisciplinary team of researchers working together with an NHS ethical review board, 50 participants/people with multiple sclerosis, a team of MBSR instructors and a range of multiple sclerosis clinicians. We used mixed methods as a means to answer a complex set of research questions about the feasibility and likely effectiveness of mindfulness-based interventions for people with multiple sclerosis. We were able to publish a suite of peer reviewed papers through this process and are now well placed to apply for funding for a large-scale trial.

Classroom Discussion Questions

1. What are the benefits of using a mixed methods approach to answering complex research questions?
 2. Should feasibility research follow a predictable, linear process?
 3. Why/how should researchers seek to involve people affected with a given condition in clinical research?
 4. Is it ethical to carry out feasibility research and not proceed to a full-scale trial if initial findings suggest likely effectiveness?
 5. What does it mean when participants describe benefits from an intervention, but none are apparent on quantitative testing?
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Multiple Choice Quiz Questions

1. The MRC framework for developing and evaluating complex interventions is
 - a. Exclusively designed for drug trials
 - b. A purely quantitative approach to research
 - c. A flexible, mixed-methods approach designed to help answer complex research questions in healthcare CORRECT

2. Mixed-methods research refers to
 - a. Research that mixes up researchers
 - b. Research that mixes research with clinical practice
 - c. Research that typically uses both quantitative and qualitative approaches
CORRECT
 3. Feasibility studies
 - a. Typically take place once a full-scale trial is complete
 - b. Tell us whether an intervention is effective
 - c. Ideally take place prior to and inform design of a full-scale trial
CORRECT
 4. Systematic reviews
 - a. Must be purely quantitative
 - b. Should have a registered protocol available once completed
 - c. Should have a registered protocol available in advance CORRECT
 5. Epidemiology
 - a. Is about how often diseases occur in different groups of people and why
CORRECT
 - b. Is purely for qualitative researchers
 - c. Is a form of thematic analysis
-

Declaration of Conflicting Interests

“The Author(s) declare(s) that there is no conflict of interest.”

Further Reading

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2. Moore, Graham F., et al. "Process evaluation of complex interventions: Medical Research Council guidance." *bmj* 350 (2015): h1258.
3. Petticrew, Mark, and Helen Roberts. *Systematic reviews in the social sciences: A practical guide*. John Wiley & Sons, 2008.
4. Thabane, Lehana, et al. "A tutorial on pilot studies: the what, why and how." *BMC medical research methodology* 10.1 (2010): 1.
5. Ritchie, Jane, and Liz Spencer. "Qualitative data analysis for applied policy research." *Analyzing qualitative data*. Routledge, 2002. 187-208.

Web Resources

1. The Equator Network - <http://www.equator-network.org/>

2. The PRISMA statement - <http://www.prisma-statement.org/>
3. The CONSORT checklist - <http://www.consort-statement.org/>
4. My thesis - <http://theses.gla.ac.uk/7893/1/2017simpsonphd.pdf>

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